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Comparison of propaten heparin-bonded vascular graft with distal anastomotic patch versus autogenous saphenous vein graft in tibial artery bypass

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Abstract

Introduction: Heparin-bonded expanded polytetrafluoroethylene grafts (Propaten, WL Gore, Flagstaff, AZ, USA) have been shown to have superior patency compared to standard prosthetic grafts in leg bypass. This study analyzed the outcomes of Propaten grafts with distal anastomotic patch versus autogenous saphenous vein grafts in tibial artery bypass.

Methods: A retrospective analysis of prospective collected data was performed during a recent 15-year period. Sixty-two Propaten bypass grafts with distal anastomotic patch (Propaten group) were compared with 46 saphenous vein graft (vein group). Pertinent clinical variables including graft patency and limb salvage were analyzed.

Results: Both groups had similar clinical risk factors, bypass indications, and target vessel for tibial artery anastomoses. Decreased trends of operative time (196 $\pm$ 34 min vs. 287 $\pm$ 65 min, $p = 0.07$) and length of hospital stay (5.2 $\pm$ 2.3 days vs. 7.5 $\pm$ 3.6, $p = 0.08$) were noted in the Propaten group compared to the vein group. Similar primary patency rates were noted at four years between the Propaten and vein groups (85%, 71%, 64%, and 57%, vs. 87%, 78%, 67%, and 61% respectively; $p = 0.97$). Both groups had comparable secondary patency rates yearly in four years (the Propaten group: 84%, 76%, 74%, and 67%, respectively; the vein group: 88%, 79%, 76%, and 72%, respectively; $p = 0.94$). The limb salvage rates were equivalent between the Propaten and vein group at four years (84% vs. 92%, $p = 0.89$). Multivariate analysis showed active tobacco usage and poor run-off score as predictors for graft occlusion.

Conclusions: Propaten grafts with distal anastomotic patch have similar clinical outcomes compared to the saphenous vein graft in tibial artery bypass. Our data support the use of Propaten graft with distal anastomotic patch as a viable conduit of choice in patients undergoing tibial artery bypass.

Keywords

PTFE graft, lower leg bypass, distal anastomotic vein patch, Propaten, heparin-bonded graft, saphenous vein graft, tibial artery bypass

Introduction

The prevalence of lower extremity arterial occlusive disease has increased steadily in recent decades due to the rise of the aging population in the USA. For patients who require lower leg arterial bypass reconstruction, autogenous vein graft remains the ideal bypass conduit because of its vessel compliance and clinical efficacy. In patients whose saphenous veins were either unsuitable or unavailable, prosthetic grafts such as expanded polytetrafluoroethylene (ePTFE) become an alternative conduit of choice. While studies have shown that ePTFE grafts produced equivalent clinical outcomes compared to autogenous saphenous vein graft in above-knee femoropopliteal artery bypass, its patency rate is significantly decreased when utilized in infrageniculate or tibial artery revascularization.[1,2]

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In an effort to improve prosthetic graft performance in small caliber vessels such as tibial artery revascularization, researchers have developed various adjunctive strategies including distal anastomotic vein patch and arteriovenous fistula to reduce graft failure rate.[3–6] Advances in biomaterial science have similarly led to heparin-bonding technology to further improve graft patency by reducing platelet deposition and decreasing graft thrombogenicity. We have previously reported the beneficial role of heparin-coated ePTFE prosthetic graft in both canine and baboon interposition bypass grafting models which showed a reduction of intimal hyperplasia and improvement of bypass patency.[7,8] Since the introduction of a bioactive ePTFE graft utilizing Carmeda heparin-bonded technology (Carmeda, WL Gore, Flagstaff, AZ, USA) with covalent end point attachment of heparin, its clinical efficacy in terms of improvement of early graft patency has been reported in multiple large clinical studies.[9–12] A recent clinical study comparing heparin-bonded PTFE graft and saphenous vein grafts for below-knee bypass demonstrated comparable patency rates between the two bypass groups.[13] The purpose of this study is to analyze our own experience with tibial artery revascularization using heparin-bonded ePTFE graft with distal anastomotic patch and autogenous saphenous vein conduits.

Patients and methods

A retrospective review of a prospectively collected database was performed for all patients undergoing tibial artery bypass from January 2001 to June 2016 at two university-affiliated academic medical centers. Appropriate Institutional Review Board protocol approval for medical record review was obtained. Patients analyzed include those who underwent femoro-tibial artery bypass with heparin bonded ePTFE graft (Propaten Gore-Tex graft, W.L. Gore, Flagstaff, AZ, USA) with distal anastomotic vein patch or great saphenous vein graft. Patients with the following criteria were excluded from the analysis: 1) saphenous vein graft in composite or sequential bypass, 2) saphenous vein graft was spliced from multiple segments, 3) concomitant endovascular interventions to improve iliac inflow, 4) the use of arm vein, or 5) the use of cadaveric saphenous vein graft.

Pertinent clinical variables were recorded which included patient demographic data, medical comorbidities, indications, bypass anatomy, and prior bypass. Diabetes mellitus was identified as patients requiring oral hypoglycemic medication or insulin therapy. Indications included claudication (Rutherford 3), rest pain (Rutherford 4), nonhealing ulceration (Rutherford 5), and gangrene (Rutherford 6). All patients underwent preoperative venous ultrasound for vein mapping. Saphenous vein graft was harvested for bypass if the diameter was greater than 2.5 mm. For patients undergoing saphenous vein interposition bypass grafting, open skip incisions were used for vein harvest, particularly around the knee and upper thigh regions. For those undergoing prosthetic grafting, 6mm Propaten graft was used in all cases. The distal anastomotic patch was created using either autogenous saphenous patch or bovine pericardium patch (Cryolife, Kennesaw, GA, USA). The distal anastomotic patch was created based on a previously published technique.[6] Sterile tourniquet technique was used in all patients for all tibial or peroneal anastomosis as a means of distal vascular control.

All patients were discharged on antiplatelet medication with 81 mg of aspirin. Additional anticoagulation was given based on clinical considerations. For patients who were on Plavix or coumadin for cardiac reasons, their anticoagulation was resumed three days following the bypass operation. Postoperative ultrasound surveillance along with ankle-brachial index (ABI) was performed at 1, 3, 6, 12 months, and every 6 months thereafter. Criteria which define impending graft failure were based on the modified Strandness criteria for saphenous or prosthetic graft.[14] Follow-up endovascular intervention was performed if duplex ultrasound detected intraluminal stenosis in the bypass graft or post-operative leg ischemia occurred. Acute graft thrombosis was treated with percutaneous thrombectomy or thrombolysis with possible percutaneous transluminal angioplasty, whereas anastomotic stenosis was treated only with balloon angioplasty. For patients operated on bilaterally, each side was considered as a separate case in the statistical analysis.

Follow-up data were analyzed in terms of primary and secondary graft patency, limb salvage, and survival with Kaplan–Meier analysis. Limb salvage was defined as the absence of any amputation proximal to a transmetatarsal level. The results in the two groups were compared by means of log-rank test. Univariate and multivariate analysis (Cox's regression) of the factors affecting primary graft patency were performed. The association between two groups was evaluated by the odds ratio (OR) and its 95% confidence interval (CI). In Cox regression analysis, the factors with statistical significance at univariate analysis were included. Statistical significance was defined as a $p < .05$.

Results

A total of 103 patients underwent 108 tibial artery bypass operations during the study period. Sixty-two tibial artery revascularizations were performed in 59 patients with heparin-bonded ePTFE Propaten grafts (Propaten group), while 46 tibial artery bypasses were

performed in 44 patients using saphenous vein grafts (vein group). Thirteen bypass operations were not included from the database due to one or more exclusion criteria. Among the patients who underwent Propaten bypass grafting, saphenous veins were either unsuitable or unavailable in 55 patients (93%), with reasons including prior harvest for coronary artery bypass ($n = 9$, 15%), vein stripping ($n = 15$, 25%), sclerotic vein segment ($n = 18$, 31%) or inadequate vein caliber ($n = 13$, 22%).

No significant difference was found between the two groups with regards to preoperative and postoperative ankle-brachial index, race, comorbidities, baseline medication, bypass indication, and Rutherford classification (Table 1). Pedal artery run-off status did not differ significantly between the Propaten and

Table 1. Comparison of clinical characteristics between Propaten group and vein group.

Characteristics	Propaten Group ($n = 62$)	Vein group ($n = 46$)	p Value
Age, mean ± SD (years)	73 ± 11.6	75 ± 13.4	0.96
Age, range (years)	56–81	54–85	
Gender			0.86
Male	41 (66%)	28 (61%)	
Female	21 (34%)	18 (39%)	
Ankle-brachial index (mean ± SD)			
Before bypass	0.56 ± 0.7	0.48 ± 0.9	0.76
After bypass	0.94 ± 0.5	0.91 ± 0.7	0.89
Race			0.46
Caucasian	45 (73%)	32 (70%)	
Hispanic	12 (19%)	10 (22%)	
African American	3 (5%)	2 (4%)	
Asian	2 (3%)	1 (2%)	
Other	0	1 (2%)	
Comorbidities			
Hypertension	46 (74%)	36 (78%)	0.76
Diabetes mellitus	32 (52%)	26 (57%)	0.69
Hyperlipidemia	17 (27%)	15 (33%)	0.57
Coronary artery disease	22 (36%)	16 (35%)	0.69
Renal failure	9 (15%)	10 (22%)	0.57
Prior tobacco usage	32 (52%)	19 (41%)	0.74
Current tobacco usage	6 (10%)	6 (13%)	0.78
Previous failed leg bypass	7 (11%)	4 (9%)	0.69
Baseline medications			
Aspirin	55 (89%)	40 (87%)	0.94
Statin	41 (66%)	25 (54%)	0.73
Beta-blocker	41 (66%)	26 (57%)	0.58
Warfarin	10 (16%)	5 (11%)	0.48
Clopidogrel	6 (10%)	4 (9%)	0.84
Any antiplatelet	7 (11%)	3 (7%)	0.51
Bypass indication			0.63
Claudication	10 (16%)	6 (13%)	
Rest pain	23 (37%)	18 (39%)	
Tissue Loss	29 (47%)	22 (48%)	
Rutherford disease category			0.24
Rutherford 2	1 (2%)	0	
Rutherford 3	20 (32%)	10 (22%)	
Rutherford 4	15 (24%)	14 (30%)	
Rutherford 5	18 (29%)	18 (39%)	
Rutherford 6	8 (13%)	4 (9%)	
No. of distal runoff vessels			0.09
One	11 (18%)	12 (26%)	
Two	28 (45%)	14 (30%)	
Three	23 (37%)	20 (44%)	

SD, standard deviation

Table 2. Comparison of clinical and operative variables comparison between Propaten group and vein group.

Variables	Propaten group ($n = 62$)	Vein group ($n = 46$)	p Value
Leg treated			0.72
Right	29 (47%)	24 (52%)	
Left	33 (53%)	22 (48%)	
Operative time (minutes ± SD)	196 ± 34	287 ± 65	0.07
Length of hospitalization (days ± SD)	5.2 ± 2.3	7.5 ± 3.6	0.08
Proximal anastomotic vessel			0.04
External iliac artery	3 (5%)	0	
Common femoral artery	59 (95%)	26 (57%)	
Superficial femoral artery	0	17 (37%)	
Popliteal artery	0	3 (7%)	
Distal anastomotic vessel			0.57
Anterior tibial artery	14 (23%)	13 (28%)	
Tibioperoneal trunk	9 (14%)	12 (26%)	
Peroneal artery	17 (27%)	10 (22%)	
Posterior tibial artery	22 (36%)	11 (24%)	

SD, standard deviation

vein bypass group. Forty-two cases with ulcers underwent postoperative surgical wound debridement, whereas 22 cases with gangrene needed either toe or transmetatarsal amputations. Pertinent operative variables between the two groups are displayed in Table 2. Shorter operative time (196 ± 34 min vs. 287 ± 65 min, $p = 0.07$) and decreased length of hospital stay (5.2 ± 2.3 days vs. 7.5 ± 3.6, $p = 0.08$) were noted in the Propaten group compared to the vein group, although the difference did not reach a statistical significance. Analysis of the proximal anastomotic vessel showed significant difference between the two groups (Table 2). In the Propaten group, 95% of the proximal anastomosis was connected to the common femoral artery, in contrast to 57% in the vein group. In the vein group, 37% of the proximal anastomosis was derived from the superficial femoral artery, while no proximal anastomosis in the Propaten group was attached to the superficial femoral artery. This is due in part to the limited length consideration frequently encountered when using saphenous vein grafts. Similarly, 7% of the vein group originated from the popliteal artery in contrast to none in the Propaten group. No difference in the distal anastomotic vessel was found in the two groups (Table 2). In the Propaten group, distal anastomotic patch was created using autogenous saphenous patch in 36 cases (58%) and bovine pericardium patch in 26 cases (42%). With regards to the distal anastomotic patch material, there was no difference in the patency rate between the saphenous vein versus bovine pericardial patch.

There was no difference in the 30-day postoperative complication rates between the Propaten and vein group which were 5% and 7%, respectively (NS). In the Propaten group, there were two wound complications and one groin hematoma which required surgical evacuation. In the vein group, two patients developed wound dehiscence from the saphenous vein harvest site while one patient developed postoperative bleeding which required surgical repair to achieve hemostasis. During the follow-up period, graft occlusion in the Propaten and the vein group occurred in 17 and 15 cases, respectively. In 13 of these Propaten graft occlusion cases, endovascular interventions with thrombolytic therapy were successful in restoring the graft flow which revealed stenosis in the distal anastomosis. Percutaneous balloon angioplasty was performed successfully in seven of these cases to maintain the graft flow. A similar effort of endovascular interventions was performed in six vein graft occlusion cases of which it was successful only in three cases.

The two groups had equivalent annual primary graft patency rates in four years (the Propaten group: 85%, 71%, 64%, and 57%, respectively; the vein group: 87%, 78%, 67%, and 61% respectively; $p = 0.97$, Figure 1). Both groups had comparable secondary patency rates yearly in four years (the Propaten group: 84%, 76%, 74%, and 67%, respectively; the vein group: 88%, 79%, 76%, and 72%, respectively; $p = 0.94$; Figure 2). The limb salvage rates were equivalent between the two groups (the Propaten group: 93%, 92%, 88%, and 84%; the vein group: 91, 88%, 84%, and 82%; $p = 0.89$; Figure 3). Univariate analysis of primary patency for these bypass grafts showed that foot ulcers, active tobacco user, and poor run-off score of 0–1 were associated with this outcome. Multivariate analysis identified active tobacco usage and poor run-off score as predictors for graft occlusion (Table 3).

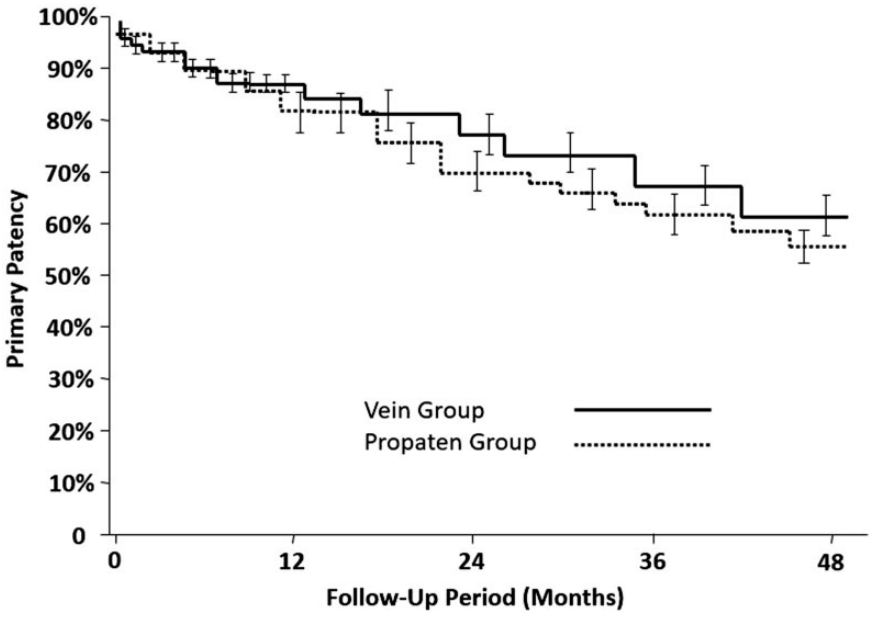

Figure 1. Comparison of primary patency of Propaten group vs. vein group using Kaplan–Meier survival curves with log-rank analysis

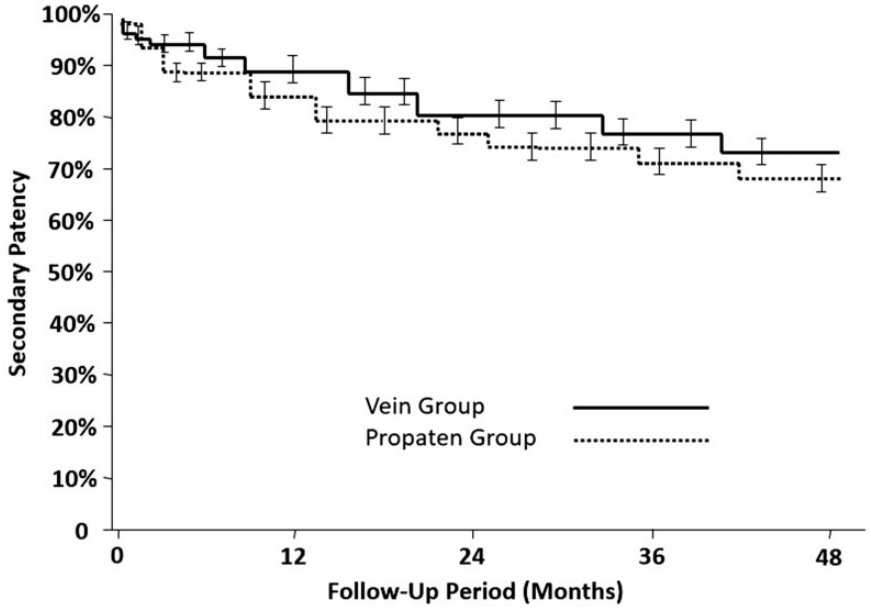

Figure 2. Comparison of secondary patency of Propaten group vs. vein group using Kaplan–Meier survival curves with log-rank analysis

Discussion

Although the ideal bypass conduit for lower leg revascularization is an autogenous saphenous vein conduit, it is estimated that up to 40% of patients with chronic limb ischemia do not have suitable saphenous vein graft for interposition bypass grafting.[15] The introduction of prosthetic bypass graft by Voorhees in 1940 and subsequent development of ePTFE conduits in the 1970s expanded the bypass graft conduit options in lower extremity revascularization.[16] Despite advances in biomaterial science, patency rate of prosthetic bypass graft remains inferior compared to autogenous vein grafts,

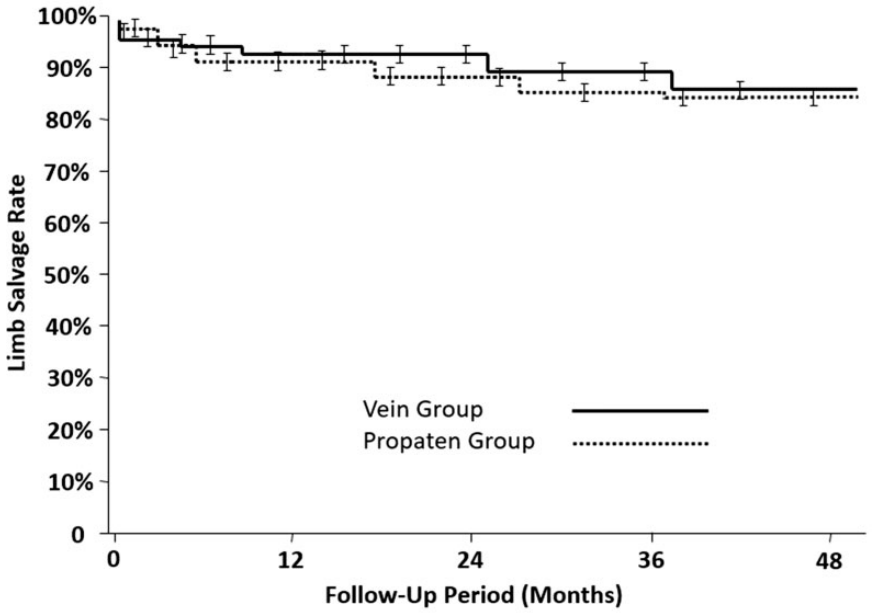

Figure 3. Kaplan–Meyer estimates of limb salvage rates between the Propaten group and the vein group.

Table 3. Univariate and multivariate analysis for primary patency during follow-up.

	Univariate Analysis				Multivariate Analysis		
	Log-rank	P	95% CI	OR	95% CI	OR	P
Renal insufficiency	0.8	0.7	0.6–2.8				
Renal failure requiring dialysis	1.2	0.6	0.4–2.7				
Diabetes	0.5	0.9	0.3–3.2				
Claudication	0.2	0.8	0.5–2.5				
Rest pain	4.5	0.02	1.3–5.4				
Foot ulcers	5.6	0.05	0.3–2.1	2.75			
History of tobacco usage (>20 pack-year)	2.4	0.1	0.4–3.7				
Active tobacco user	6.8	0.05	1.1–4.5	3.14	0.6–2.3	1.4	0.05
Warfarin therapy	1.9	0.2	0.2–1.7				
Antiplatelet therapy	0.8	0.5	0.7–2.9				
Run-off score 0–1	7.4	0.03	0.3–0.9	4.26	1.3–5.3	1.8	0.02
Run-off score 2–3	2.4	0.2	0.6–2.4				
Rutherford class 5–6	1.8	0.7	1.3–4.5				

CI, Confidence interval; OR, odds ratio

especially in infra-popliteal or tibial artery bypass. The findings of our study are notable because it demonstrated that combing the heparin-bonded Propaten bypass graft with a distal anastomotic patch can achieve similar outcomes compared to autogenous vein conduits in infra-popliteal artery bypass.

Researchers have made significant advances in recent years to improve prosthetic bypass graft patency by modifying biomaterial surface with heparin bonding technology.[17,18] We have previously reported the improved patency of heparin-coating biomaterial including both ePTFE graft and stent with resultant reduction in thrombogenicity and intimal hyperplasia in *in vivo* models.[7,8] Improved graft patency and reduced thrombogenicity with sustained heparin bioactivity at six months was also reported in a sheep carotid artery bypass model using heparin-coated ePTFE graft.[19] Other researchers have shown that heparin bonding using CBAS technology with covalent end point attachment of heparin to the luminal surface of the ePTFE graft can maintain heparin bioactivity at 16 weeks while sustaining thromboresistant property.[20] The bioactivity of heparin-bonded ePTFE surface with resultant decreased platelet adherence, decreased

thrombus formation, and reduced inflammatory response have also been shown in extracorporeal circuits, and heart-assist devices up to two years.[21–23]

The patency rates of the Propaten graft in our series was 71% at two years and 57% at four years, which were consistent with other reported series of institutional experience using heparin-bonded femoropopliteal bypass grafts. Our study showed similar clinical patency between the saphenous vein grafts and Propaten grafts with distal anastomotic patch. The one-year primary patency in prior studies using heparin-bonded ePTFE graft ranged from 71.6% to 92%.[4,9–11,13,24–31] Peeters et al. reported two-year patency rates of 73% for below-knee bypass and 69% for tibial bypass using heparin-bonded ePTFE grafts.[31] A multicenter Italian registry analyzed 425 patients undergoing infrainguinal bypass using heparin-bonded ePTFE graft for critical limb ischemia, and reported primary patency, secondary patency, and limb salvage rates at 36 months of 61%, 70%, and 83%, respectively. The patient cohorts in this study included 20% tibial artery bypass with an overall one-year patency rate of 75%.[11] The Propaten European Product Evaluation (PEPE II) multicenter prospective European registry observed 12-month primary patency rates of 82.7% in above-knee and 74.2% in below-knee heparin-bonded femoropopliteal grafts.[25] A prospective randomized multi-institutional Scandinavian study documented a 12-month primary patency rate of 80.4% in the heparin-bonded femoropopliteal grafts, which was a significant improvement over the 69.6% rate observed in the standard ePTFE group of that study.[27] In comparison, Daenens et al. reported higher patency for heparin-bonded ePTFE grafts versus vein grafts in below-knee bypasses and concluded that heparin-bonded ePTFE should be routinely considered for below-knee bypass.[13] In contrast, Dorigo et al compared primary patency for in situ vein, standard PTFE, and heparin-bonded ePTFE in a below-knee bypass experience, and reported patency rates at 18 months of 75% for vein, 40% for standard PTFE, and 53% using heparin-bonded ePTFE.[32] Although the results represented a 57% reduction in early graft thrombosis when using heparin-bonded ePTFE, the authors noted that saphenous vein grafts remained superior when compared to prosthetic graft conduits.[32]

In an effort to improve prosthetic bypass graft patency in small caliber vessels such as the tibial artery, researchers have investigated various anastomotic techniques to improve graft performance and enhance anastomotic compliance. Distal vein patch in the arterial anastomotic site has been a widely described technique to improve the hemodynamic compliance in the graft-artery interface. In our series, we utilized the saphenous vein as a patch material in 58% and used the bovine pericardium patch in the remaining 42% of cases (Figure 4). Although we prefer the saphenous vein as the patch material of choice, more than 93% of patients in our series do not have suitable or available saphenous veins. In our practice, the bovine pericardium is an invaluable alternative patch material for distal anastomotic patch reconstruction when the saphenous vein is unusable or unavailable. We found the quality and thickness of a bovine patch material to be more consistent and reliable compared to autogenous saphenous veins. The elastic nature and ease of handling of sutures in a bovine pericardial patch is similar to that of an autogenous vein patch. The safety and efficacy of using the bovine pericardial patch in vascular reconstruction has been widely reported previously, particularly in carotid endarterectomy.[33–36]

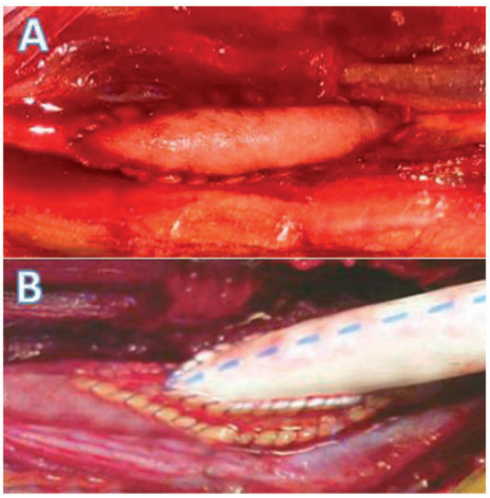

Figure 4. (a) A distal arterial patch is created in the tibial artery in all Propaten group. (b) Following the patch creation, the Propaten PTFE graft is connected to the tibial anastomotic patch in an end-to-side fashion to complete the tibial artery anastomotic reconstruction.

The clinical outcomes of tibial artery bypass using interposition prosthetic bypass grafting with the distal anastomotic vein patch have been studied previously.[4,5,24,29,37] Neville and associates reported their experience of 121 patients with tibial artery bypass using ePTFE graft with distal vein patch, and noted a primary patency rate at four years was 51%.[29] Bellosta analyzed distal vein patch, the vein cuff, and pre-cuffed ePTFE reconstructive techniques and showed that distal anastomotic patch provided better results compared to the other two anastomotic configurations.[3] A European prospective study analyzed 86 patients who underwent either PTFE interposition bypass grafting with vein patch versus autogenous vein bypass graft, and it showed improved primary patency and limb salvage rate using distal vein patch as compared to PTFE bypass grafting alone. The authors recommended interposition grafting with distal anastomotic

vein patch as the treatment strategy in patients who do not have adequate autogenous vein conduit.[4]

Our results showed similar graft patency rate between the two groups at three-year follow up. Additionally, the limb salvage rate was similar between the two groups. Although previous studies have suggested increased graft infection rate with lower extremity prosthetic interposition grafting in patients with non-healing ulcers or gangrenous wounds, our results showed no difference in graft infection between the two groups. We attribute this to aggressive wound debridement and expeditious wound closure with liberal use of negative-pressure wound therapy along with appropriate intravenous antibiotic coverage.

Several weaknesses undoubtedly exist in our study. First, the group comparison was performed in a retrospective non-randomized fashion, which was clearly associated with selection bias among patient cohorts. Additionally, the distal anastomotic vein patch was performed either with an autogenous saphenous vein or a bovine pericardial patch if no suitable vein conduit was available. The difference in these two patch materials, while performed with identical surgical technique in distal anastomotic patch creation, may render different hemodynamic responses and subsequently graft performance. Lastly, the reconstructive method of prosthetic bypass grafting with distal anastomotic patch creation is a highly complex process involving numerous technical variabilities. Technical variables such as the beveled angle of prosthetic graft attached to the vein patch, the choice of suture, and the use of tourniquet versus tibial artery clamps were largely based on the surgeon's preference, which can inevitably influence the treatment outcome. Notwithstanding these limitations, the comparable patency rate of heparin-bonded ePTFE graft with distal anastomotic patch reconstruction versus saphenous vein graft remains a significant finding in our study.

In conclusion, our study showed comparable treatment outcome between prosthetic bypass grafting with distal anastomotic patch versus interposition grafting with autogenous saphenous vein conduit at three years of follow-up. Although this finding suggests heparin-bonded ePTFE graft with distal anastomotic patch is an effective alternative when an autogenous saphenous vein conduit is not available for tibial artery revascularization, further randomized studies with larger patient size are warranted to further validate the outcome of this treatment modality.

Declaration of conflicting interests

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